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Title: Dynamic relationship between D-dimer and COVID-19 severity

Running Title: D-dimer level varies as COVID-19 progresses

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KEY POINTS :

1. The dynamic changes of D-dimer level were positively correlated with the severity of COVID-19.
2. Anticoagulant treatment may reduce the mortality of COVID-19 patients, especially those without cardiovascular diseases.

Collectively, dynamic observation of D-dimer can help to predict the progression of COVID-19. In addition, anticoagulant treatment may be beneficial for critical COVID-19 patients, even those without cardiovascular disease.

KEY WORDS :

coagulation parameter, D-dimer, COVID-19, anticoagulant treatment

Letter to the editor :

Since December 2019, the seriousness of coronavirus disease 2019 (COVID-19) pandemic has been on escalation (Lu, *et al* 2020). Coagulopathy is common in critically ill patients with COVID-19 (Tang, *et al* 2020b). Systemic microvascular thrombosis may occur in most deaths, which was further identified by a recent autopsy (Luo 2020). However, less has been known about the coagulation parameter D-dimer in the progression of COVID-19. In this study, we describe 279 COVID-19 patients recruited from three hospitals in Hubei Province, China, and then investigate the dynamic relationship between D-dimer level and the progression of COVID-19.

According to COVID-19 Diagnosis and Treatment Scheme (Trial Version 7) (Commission 2020), all laboratory-confirmed COVID-19 patients were mild and moderate cases on admission in our study. We further divided them into three groups according to their clinical courses: ordinary group (disease was mild or subsided, $n=136$); improved group (disease worsened first and was then improved gradually after treatment, $n=23$); poor group (disease deteriorated and deaths, $n=120$). On admission, the epidemiological data, comorbidities, and clinical symptoms of patients were obtained (**Table 1**). Then, we tested coagulation profile for ten consecutive days since admission.

As shown in **Table 1**, the median age of 279 enrolled patients was 55.0 (IQR 39.0–68.0), highest in poor group, followed by improved group. Cardiovascular disease ($n=77$, [27.6%]), respiratory disease ($n=29$, [10.4%]), and endocrine disease ($n=35$, [12.5%]) were the most common comorbidities.

Infection-induced coagulopathy and secondary hyper-fibrinolysis has been identified in severe cases of COVID-19 (Ji, *et al* 2020). As well, higher D-dimer level on admission was related to a worse prognosis of COVID-19 (Zhou, *et al* 2020). Thus, we tracked the variations of D-dimer for ten consecutive days. Based on random forests, Gini index at Day 1 was obviously higher than that at the other days in three groups (**Figure 1a**). On admission, D-dimer level was higher in improved and poor groups than that in ordinary group. Then, the level decreased gradually in improved group, but remained high in poor group as the disease deteriorated (**Figure 1b**). The results were further adjusted and examined by multinomial logistic regression model. As shown in **Figure 1c**, on admission, compared with ordinary group, improved group and poor group demonstrated an odds ratio (OR) of 1.42 (95% CI: 1.04, 1.96, $p=0.03$) and 1.35 (95% CI: 1.02, 1.80, $p=0.04$), respectively (**Table S1**). 0.93 (0.78, 1.10)

Further, we separated the ten days into three stages: Stage 1, Day 1; Stage 2, Day 2-5; Stage 3, Day 6-10. At Stage 1, OR of ordinary group (0.25 (95% CI: 0.16, 0.37, $p<0.001$)) was obviously different from that of poor group (0.93 (95% CI: 0.78, 1.10, $p=0.37$)) (**Figure 1d, e**). From Stage 1 to Stage 2, D-dimer level increased with disease progression in poor group (1.60 (95% CI: 1.28, 2.00, $p<0.001$)), but not in ordinary group (1.19 (95% CI: 0.97, 1.46, $p=0.09$)) (**Figure 1d, e**). The same trend from Stage 2 to Stage 3 was also observed, and the OR of ordinary group and poor group was 1.25 (95% CI: 1.07, 1.47, $p=0.07$), and 1.71 (95% CI: 1.43, 2.05, $p<0.001$), respectively (**Figure 1d, e**). The detailed information was shown in **Table S2**.

Pulmonary thrombosis is most responsible for the elevation of D-dimer in severe cases (Wang, *et al* 2011). Although more evidence is needed, our finding is meaningful for the establishment of early diagnosis and dynamic intervention.

Moreover, it has been well documented that abnormal D-dimer is helpful in indicating deep venous thrombosis in cardiovascular diseases (Giannitsis, *et al* 2017). Thus, we analysed the correlation between D-dimer level with clinical prognosis inpatients with/without cardiovascular disease. First, there was a difference in D-dimer levels of patients with and without cardiovascular disease in the poor group ($p=0.047$) (**Table S3**). Then, among patients with cardiovascular disease in the poor group, no difference was observed between non-survivors and survivors ($p=0.83$). Last, among patients without cardiovascular disease in the poor group, non-survivors had higher D-dimer levels than survivors ($p=0.02$).

As for the current therapeutic regimens for COVID-19, no effective antivirals and vaccines have yet been recommended for patients with COVID-19. A previous report claimed that a D-dimer level $> 1\mu\text{g/mL}$ was associated with a lower mortality after heparin treatment (Tang, *et al* 2020a). Thus, anticoagulant treatment appears to be beneficial in severe COVID-19 cases. Given that non-survivors had higher D-dimer than survivors among the patients without cardiovascular diseases in the poor group, timely and effective anticoagulant treatment may be workable.

When administering anticoagulant treatment, enough attention should be paid to diffuse alveolar hemorrhage (DAH), which is a life-threatening complication after warfarin use (Kiyota and Shiota 2019). Thus, international normalized ratio (INR) should be used for early diagnosis and rapid therapeutic intervention.

Overall, the dynamic changes of D-dimer level is positively correlated with the prognosis of COVID-19. Anticoagulant treatment may benefit severe COVID-19 patients, especially those without cardiovascular diseases.

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AUTHOR CONTRIBUTIONS

Drs Yong Li, Kun Zhao, Hongcheng Wei, Wensen Chen, Zhihang Peng, Yun Liu and Xiaoxiang Yan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Drs Yong Li, Zhihang Peng, Yun Liu and Xiaoxiang Yan. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Drs Yong Li, Zhihang Peng, Yun Liu and Xiaoxiang Yan. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Drs Yong Li, Kun Zhao, Hongcheng Wei, Wensen Chen, Zhihang Peng, Yun Liu and Xiaoxiang Yan. Supervision: Drs Yong Li and Xiaoxiang Yan.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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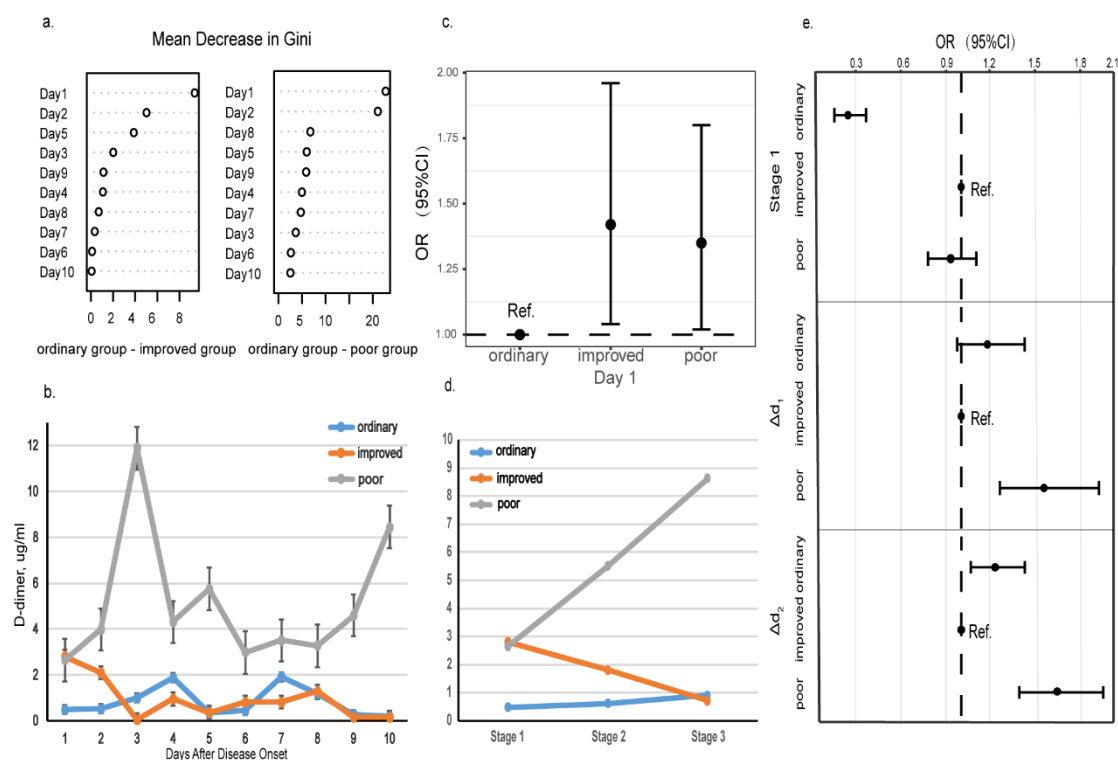


Figure 1: Association between D-dimer and COVID-19 Progression

Figure 1a: Feature importance based on random forest (left, ordinary group and improved group; right, ordinary group and poor group).

Figure 1b: Variations of D-dimer for ten consecutive days from disease onset.

Figure 1c: Odds ratio of prognosis associated with 1 $\mu\text{g/mL}$ increment in D-dimer level on admission.

Figure 1d: Variations of D-dimer from Stage 1 to Stage 3.

Figure 1e: Odds ratio of prognosis associated with 1 $\mu\text{g/mL}$ increment in D-dimer level at Stage 1, from Stage 1 to Stage 2 (Δd_1) and from Stage 2 to Stage 3 (Δd_2), respectively.

Table 1: Baseline characteristics and laboratory findings of patients infected with COVID-19 on admission.

Characteristics	No. (%)				p
	Total (N=279)	ordinary (n=136)	improved (n=23)	poor (n=120)	
Age, median (IQR), years	55 (39-68)	49 (36-56)	58 (41.5-67.5)	65 (51-72)	<0.001
Sex					
Male	149 (53.4)	66 (48.5)	12 (52.2)	71 (59.2)	0.31
Female	126 (45.2)	67 (49.3)	10 (43.5)	49 (40.8)	
Cardiovascular disease	77 (27.6)	25 (18.4)	1 (4.3)	51 (42.5)	<0.001
Respiratory disease	29 (10.4)	10 (7.4)	1 (4.3)	18 (15.0)	0.08
Immune disease	7 (2.5)	3 (2.2)	0 (0.0)	4 (3.3)	0.61
Endocrine disease	35 (12.5)	12 (8.8)	1 (4.3)	22 (18.3)	0.03
Tumour	3 (1.1)	1 (0.7)	0 (0.0)	2 (1.7)	0.67
Infectious disease	9 (3.2)	2 (1.5)	1 (4.3)	6 (5.0)	0.27
Signs and symptoms					
Fever	217 (77.8)	106 (77.9)	17 (73.9)	94 (78.3)	0.53
Cough	191 (68.5)	99 (72.8)	17 (73.9)	75 (62.5)	0.54
Chest tightness	31 (11.1)	16 (11.8)	1 (4.3)	14 (11.7)	0.15
Shortness of breath	24 (8.6)	7 (5.1)	3 (13.0)	14 (11.7)	0.02
Fatigue	60 (21.5)	27 (19.9)	9 (39.1)	24 (20.0)	0.13
Heart rate, median(IQR), bpm	86 (80-98)	86 (80-98)	87.5 (72-95)	88 (80-98)	0.26
SBP, median(IQR), mm Hg	125 (119-137)	125 (118-136.5)	121 (116-130)	126 (120-139)	0.73

DBP, median(IQR), mm Hg	78 (70-86)	80 (76-87.5)	79 (70-85)	75 (70-80)	<0.001
Respiratory rate, median(IQR)	20 (19-22)	20 (18-20)	20 (20-22)	20 (20-25)	<0.001
Laboratory indexes median (IQR)					
White blood cell count, $\times 10^9/L$	5.0 (4.0-7.9)	4.2 (3.6-5.2)	4.8 (4.1-8.0)	6.6 (4.5-8.6)	<0.001
Lymphocyte count, $\times 10^9/L$	0.9 (0.6-1.3)	1.2 (0.9-1.6)	0.7 (0.7-1.3)	0.8 (0.5-1.1)	<0.001
Lactate dehydrogenase, U/L	263.0 (179.0-360.0)	186.0 (164.0-233.5)	277.0 (190.0-297.5)	335.0 (227.0-408.0)	<0.001
Alanine transaminase, U/L	23.0 (16.8-36.5)	23.0 (17.8-30.5)	21.0 (19.0-72.0)	25.0 (16.0-50.0)	<0.01
Aspartate Transaminase, U/L	27.0 (18.0-45.5)	22.0 (17.5-33.0)	27.0 (23.5-48.0)	33.0 (18.0-49.0)	0.14
Creatinine, $\mu\text{mol/L}$	73.2 (60.5-92.5)	77.0 (64.4-94.0)	54.9 (48.0-68.0)	73.9 (63.5-95.0)	0.16
Carbamide, mmol/L	5.3 (4.1, 6.9)	4.8 (3.9, 6.5)	4.4 (3.3, 5.0)	5.9 (4.9, 8.2)	0.17
D-dimer, $\mu\text{g/mL}$	0.3 (0.1-1.3)	0.2 (0.1, 0.4)	0.8 (0.6-7.3)	0.6 (0.2-5.0)	<0.01
